C1

Fig. 1A is a simplified diagram of a database system 1000 according to an embodiment of the present invention. This diagram is merely an example and should not limit the scope of the claims herein. One of ordinary skill in the art would recognize many other variations, modifications, and alternatives. Database system 1000 includes a variety of techniques for processing images from biological cells, e.g., fixed, living, and dead cells, and cell portions. As shown, images are acquired 1001. These images can be from a single frame or multiple frames. As merely an example, an image processing system may analyze such images. An example of such an image processing system is described below, but should not be construed as limiting certain claims. A further example of processing techniques is described in more detail in U.S. Serial No. 09/311,890 noted above. Each image is of a cell portion or a plurality of portions, which are digitized representation(s).

At page 45, please **replace** the paragraph beginning at line 23 and ending at line 28 with the following:

C2

An example of a MatLab program called "AnalyseDNA" that takes as an input an unlimited number of images, identifies individual objects in these images based on either their intensities, or based on edge-detection algorithms, and extracts a number of morphological and intensity characteristics of these objects. A copy of this program is described in U.S. Application Serial No. 09/310,879, which has been noted.

REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on July 16, 2001 and the Notice of Non-Compliant Amendment mailed December 31, 2001. Applicants acknowledge that the restriction requirement, mailed September 1, 2000 has been withdrawn and all presently pending claims are under examination. Claims 1-44 have been rejected. Claims 15 and 19-28 have been cancelled herein. As such, Claims 1-14, 16-18, and 29-44 are pending.

This amendment is to expedite prosecution and should not be construed as acquiescence in any ground of rejection. Applicants reserve the right to prosecute the originally filed claims in the future. The comments in the Office action are now addressed in turn.

Rejections under 35 U.S.C. § 112

Claims 1-15 and 29-39 have been rejected under 35 U.S.C.§112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter of the invention. More specifically, the Examiner has expressed concerns regarding the antecedent basis for the phrase "the plate" in Claim 1, Claim 11, and Claim 29. With regards to Claims 1 and 29, Applicants have amended the claims here to address these concerns. Applicants respectfully maintain that antecedent basis for the phrase "the plate" in Claim 11 can be found in line 2 of the claim.

In addition, the Examiner has expressed concerns regarding the phrase "the plurality of cells" in Claim 1; the phrase "one sub-element" in Claim 3, and the phrase "1X and greater" in Claim 6. Applicants have amended these claims to address the Examiner's concerns.

Applicants respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 11-14 and 16-28 have been rejected under 35 U.S.C. § 102(a) as being anticipated by U.S. Patent No. 5,733,721 ("Hemstreet"). The rejection is respectfully traversed.

As repeatedly indicated by the courts, anticipation requires that all of the elements and limitations of the claim be found within a single prior art reference. There must be no difference between the claimed invention and the disclosure provided by the reference, as viewed by a person of ordinary skill in the field of the invention. (*Scripps Clinic & Research Fdtn. v. Genentech, Inc.*, 927 F.2d 1565, 1576 [Fed. Cir. 1991]). Furthermore, "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. (*In re Royka*, 490 F.2d 981, 180 USPQ 580 [CCPA 1974]). Applicants submit that Hemstreet does not teach every element of the claims; therefore, that the invention, as claimed herein, is not anticipated by Hemstreet.

Hemstreet is cited as teaching a fluorescence imaging system with the capability of digital analysis of the cellular images. Hemstreet is also said to teach image analysis storage and retrieval and the evaluation of the samples for various criteria such as cancer risk assessment. Hemstreet lacks specifics regarding the illumination system that is used in the imaging system.

The present invention provides a system for capturing images of cells or cell structures as well as related systems for acquiring knowledge from cellular information and databases therefor. The systems of the invention are capable of analyzing a plurality of cells. Significantly, it was found that improved images could be obtained if a liquid light guide was used as the illumination apparatus. Such a liquid light guide provides for a relatively uniform illumination of the cells which is advantageous when one wants to capture an image of the cells. As noted in the Specification at page 16, a liquid light guide has less than about 30% transmission loss of the light at remote locations.

Hemstreet does not teach or suggest the use of a liquid light guide for illuminating cells for subsequent image capture. As the Examiner has noted, Hemstreet is silent as to how to illuminate cells.

As the elements of Hemstreet are *not* the same as those presently claimed, Applicants submit that Hemstreet does not anticipate the pending claims and respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-6, 8-28, 40, and 42-44 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Hemstreet in view of Sutherland *et al.* U.S. Patent No. 4,818,710 ("Sutherland"). In addition, the claims been rejected under 35 U.S.C. 103(a) as being unpatentable over Hemstreet in view of Sutherland and in further view of Balch U.S. Patent No. 6,083,763 ("Balch") or *In re Venner* (120 USPQ 193); all being taken in view of Rutenberg *et al.* U.S. Patent No. 5,287,272. This rejection is respectfully traversed.

Hemstreet is cited as above. Sutherland is cited as teaching a liquid light guide illumination system for use with microscope slide samples. Balch is said to describe the use of robotic arms for moving samples during sample preparation during assays. Venner is cited for its holding that automation of a manual method is obvious. Rutenberg is said to describe the use of barcodes on assay items.

As discussed above, the present invention is drawn to a system for capturing images of cells that utilizes a liquid light guide. Other elements of the system include an image capturing device, an image processing device, and database storage device. Other embodiments include an image capturing device, an illumination apparatus, a robotic arm, and software for analyzing the images and characterizing the features.

The shortcomings of Hemstreet have discussed above. Sutherland does not rectify these deficiencies. More specifically, Sutherland teaches the use of a light source 6 with a waveguide 8. See Fig. 2 of Sutherland. The light source is a xenon flash lamp. The analytical cell or cuvette is based on a microscope slide waveguide system. See Sutherland at column 9, lines 18-20. The waveguide 8 is actually the bottom of the microscope slide. See Sutherland at column 9, lines 20-21. An index matching oil is used between the microscope slide and the cuvette 7. Two-quarter round silica prisms 16 and 17 form the sides of the oil reservoir. See Sutherland at column 9, lines 25-27. Thus, the "liquid light guide" taught by Sutherland is an oil-filled reservoir formed by a cuvette, a microscope slide, and two silica prisms.

In contrast to Sutherland, the present specification states at page 16 that the light guide is suitably selected to have a *flexible* member, which can be used to place lamp source at a remote location away from the imaging device. The flexible member substantially keeps any vibration from the lamp assembly away from the imaging device. In some embodiments, the light guide is a *flexible* hose-type sleeve filled with a liquid such as an aqueous solution containing chloride or phosphate.

The difference between the flexible liquid light guide of claimed invention and the rigid light guide of Sutherland is further highlighted by the purposes of the two liquid guides. More

specifically, the flexible liquid light guide of the instant invention serves to insulate the imaging device from any vibration from the lamp assembly. The purpose of the Sutherland light guide is to eliminate the need for specially polished, optically flat waveguide faces. Applicants submit that a flexible light guide (as used in the instant application) would not accomplish this purpose.

Neither Hemstreet nor Sutherland, either alone or in combination, teach the use of a flexible liquid light guide in an image capturing system. None of the secondary references cure the lack of suggestion of the primary reference(s) to use a flexible liquid light guide in an image capturing system.

For these reasons, withdrawal of the rejections is respectfully requested.

Objections to the Specification and Claims

The specification and claims have been objected to because of various informalities. Applicants have amended the specification and claims as necessary to address the Examiner's concerns. In response to the Notice of Non-Compliant Amendment, Applicants have included a clean version of the replacement paragraphs.

Conclusion

The Applicant respectfully maintains that all pending claims are in condition for allowance. Therefore, the Applicant respectfully requests a Notice of Allowance for this Application from the Examiner. Should any unresolved issues remain, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP

Lauren L. Stevens
Reg. No. 36,691

P.O. Box 778
Berkeley, CA 94704-0778
(650)961-8300

MARKED UP VERSION OF AMENDED CLAIMS

1. (Amended) A system for capturing images of cells or cell structures, the system comprising:

a cell holder comprising a plurality of sites in a spatial orientation, each of the sites being capable of holding a plurality of cells to be imaged;

an image capturing device coupled to the cell holder, the image capture device being adapted to capture at least one image in at least one of the plurality of sites;

an illumination apparatus comprising a **flexible** liquid light guide coupled to the [plate] **cell holder** for highlighting **the plurality of sites** [the plurality of cells] in a relatively even spatial manner for image capturing purposes;

an image processing device coupled to the image capturing device, the image capturing device being adapted to convert the image into a digital representation; and

a database storage device comprising a database management element coupled to the image capturing device, the database storage device being adapted to retrieve the digital representation of the image from the image processing device and storing the digital representation.

3. (Amended) The system of claim 1 wherein the illumination apparatus comprises sub-elements, at least one of the sub-elements being positioned away from the image capturing device to prevent a possibility of vibration from the **at least** one **of the** sub-elements to be transmitted to the image capturing device.

6. (Amended) The system of claim 1 wherein the image capturing device comprises a magnification of at least 1X [and] **or** greater to capture the image of the site.

8. (Amended) The system of claim 1 wherein the liquid light guide **is** characterized as a flexible member that substantially prevents vibration from [the] an element of the illumination apparatus to be transferred to the image capturing device.

11. (Amended) A database system comprising:

a plate comprising a plurality of sites in a spatial orientation, each of the sites being capable of holding a plurality of cells to be imaged;

a light source comprising a flexible liquid light guide coupled to the plate for illuminating the plurality of cells in a relatively uniform spatial manner for image capture purposes;

an image capturing device to capture a plurality of images of at least one of the sites, the image capturing device coupled to the plate;

an image processing device to combine a first image and a second image from the plurality of images, the image processing device coupled to the image capturing device, the image processing device being adapted to form a plurality of respective features of the plurality of images; and

a database storage device comprising a database management element coupled to the image processing device, the database storage device being adapted to retrieve the plurality of features and store the plurality of features.

14. (Amended) The system of claim 11 wherein the image capturing device comprises a magnification of at least 1X [and] **or** greater to capture the plurality of images of the cells.

16. (Amended) A system for capturing cellular information from a population of cells, the system comprising:

an image acquisition system comprising a charged coupled camera adapted to capture an image of a plurality of manipulated cells, the illumination apparatus providing for an acquisition of the image of the plurality of manipulated cells;

an illumination apparatus **comprising a flexible liquid light guide** coupled to the image acquisition system for highlighting the plurality of manipulated cells; and

a database system coupled to the image acquisition system, the database system being adapted to be populated with information of the image of the plurality of manipulated cells;

wherein the information comprises a plurality of descriptors, each of the desciptors comprising a plurality of features, each of the features corresponding to a cellular or subcellular component from the plurality of manipulated cells.

18. (Amended) The system of claim 16 wherein each of the features provides a characteristic selected from at least a count, area, perimeter, length, breadth, fiber length, fiber breadth, shape factor, elliptical form factor, inner radius, outer radius, mean radius,

equivalent radius, equivalent sphere volume, equivalent prolate volume, equivalent oblate volume, equivalent sphere surface, average intensity, total intensity, optical density, radial dispersion, texture difference, a population statistic value, and a spatial value **of** the plurality of manipulated cells.

29. (Amended) A system for capturing images of cells or cell structures from multiple cell holders, each comprising a plurality of sites in a spatial orientation, each of the sites being capable of holding a plurality of cells to be imaged, the system comprising:

an image capturing device coupled to the cell holder, the image capturing device being adapted to capture at least one image in at least one of the plurality of sites;

an illumination apparatus comprising a **flexible** liquid light guide coupled to the [plate] **cell holder** for highlighting the plurality of cells in a relatively even spatial manner for image capturing purposes;

a robot arm for automatically collecting multiple of said cell holders to facilitate capture of the images of the cells or cell structures from said multiple cell holders; and

software that analyzes the images and characterizing features of the cells or cell structures in the images.

MARKED UP VERSION OF AMENDED SPECIFICATION

At page 1, please **replace** the section entitled "CROSS-REFERENCES TO RELATED APPLICATIONS" with the following:

The following commonly-owned co-pending applications, including this one, are being filed concurrently and the others are hereby incorporated by reference in their entirety for all purposes:

1. U.S. Patent Application Serial No. [_____] **09/310,879**, James H. Sabry, et. al., titled, "A DATABASE METHOD FOR PREDICTIVE CELLULAR BIOINFORMATICS," [(Attorney Docket Number 19681-000100US)];

2. U.S. Patent Application Serial No. [_____] **09/311,890**, James H. Sabry, et. al., titled, "A DATABASE SYSTEM FOR PREDICTIVE CELLULAR BIOINFORMATICS," [(Attorney Docket Number 19681-000200US)];

3. U.S. Patent Application Serial No. [_____] **60/134,104**, Cynthia L. Adams, et. al., titled, "A DATABASE SYSTEM AND USER INTERFACE FOR PREDICTIVE CELLULAR BIOINFORMATICS," [(Attorney Docket Number 19681-000300US)]; and

4. U.S. Patent Application Serial No. [_____] **09/311,996**, Eugeni A. Vaisberg, et. al., titled, "A DATABASE SYSTEM INCLUDING COMPUTER CODE FOR PREDICTIVE CELLULAR BIOINFORMATICS," [(Attorney Docket Number 19681-000400US)].

At page 6, please **replace** the section entitled "BRIEF DESCRIPTION OF THE DRAWINGS" with the following:

Fig. 1 is a simplified system diagram **of a cellular knowledge-based system** according to an embodiment according to the present invention;

[Figs. 1A-1B are more detailed diagrams of database systems according to embodiments of the present invention]

Fig. 1A is a simplified diagram of a database system 1000 according to an embodiment of the present invention;

Fig. 1B is a simplified diagram of a database system engine 2000 according to an embodiment of the present invention;

Fig. 2 is a simplified block diagram according to an alternative embodiment according to the present invention;

Fig. 3 is a simplified diagram of a processor or computing device 13;

Fig. 4 is a simplified diagram of an imaging system 200 according to an embodiment of the present invention;

Fig. 5 is a more detailed diagram of an imaging system 200 according to an embodiment of the present invention with the present embodiment of the imaging system being shown in Figs. 5A and 5B;

Fig. 6 is a simplified diagram 600 of a cleaning and dispensing system according to an embodiment of the present invention;

Fig. 7A illustrates a representative block flow diagram of simplified process steps of a method for determining properties of a manipulation based upon effects of the manipulation on one or more portions of one or more cells in a particular embodiment according to the present invention;

Fig. 7B illustrates a representative block flow diagram of simplified process steps for determining one or more descriptors of a state in the portions of the cells in the presence of the manipulation of step 704 of Fig. 7A in a particular embodiment according to the present invention;

Fig. 7C illustrates a representative block flow diagram of simplified process steps for obtaining images of cell portions of step 712 of Fig. 7B in a particular embodiment according to the present invention.

Fig. 7D illustrates a representative block flow diagram of simplified process steps for processing digitized representations of step 716 of Fig. 7B in a particular embodiment according to the present invention;

Fig. 7E illustrates a representative block flow diagram of simplified process steps for analyzing image feature values to obtain descriptors of cell state of step 718 of Fig. 7B in a particular embodiment according to the present invention;

Fig. 7F illustrates a representative block flow diagram of simplified process steps for a method of mapping a manipulation of cells to a physiological characteristic in a particular embodiment according to the present invention;

Fig. 7G illustrates a representative block flow diagram of a simplified process steps for a method for populating a database with manipulated biological cell information in a particular embodiment according to the present invention;

[Figs. 3-6 are simplified diagrams of system elements according to embodiments of the present invention;

Figs. 7A-7G illustrate representative block diagrams of simplified process steps in a particular embodiment according to the present invention;]

Fig. 8A-8F illustrate representative quantified descriptors of effects of manipulations on images of cells in a particular **experiment wherein Fig. 8A shows the histogram for average intensity; Fig. 8B shows histogram data for the area of each object; Fig. 8C shows the scatter plot of the average intensity vs. the area of all of the objects; Fig. 8D shows a graph where each type of cellular classification is delimited; Fig. 8E shows a bar graph of the average and standard deviations of the areas for each cell classification type; Fig. 8F shows a bar graph of the average and standard deviations of the average intensities for each cell classification type;**

Fig. 9 illustrates example images for different types of morphologies in a particular experiment;

Fig. 10 illustrates a distribution of various morphologies in a cell population responsive to drug concentration in a particular experiment;

Fig. 11 illustrates a graph of quantified features of effects of manipulations on cells in a particular experiment;

Fig. 12 illustrates effects of external agents on cells in a particular experiment;

Fig. 13 illustrates 4 panels for each marker for a plurality of A549 cells in a particular experiment;

Fig. 14 illustrates 4 panels for each marker for a plurality of OVCAR-3 cells in a particular experiment;

Fig. 15 illustrates 4 panels for each marker for a plurality of OVCAR-3 cells at 20x in a particular experiment;

Fig. 16 illustrates 4 panels for each marker for a plurality of OVCAR-3 cells at 40x in a particular experiment;

Fig. 17 illustrates a digital representation for a population module in a particular embodiment according to the present invention; and

Fig. 18 shows the results of conversion of morphometric parameters into nucleic acid code and clustering of the resulting sequences using Neighbor Joining methods;

Fig. 19 shows another example of the generation of pseudo-sequences and clustering in a particular embodiment according to the present invention.

[Figs. 18-19 illustrate examples of the generation of pseudo-sequences and clustering in a particular embodiment according to the present invention.]

At page 7, please **replace** the paragraph beginning on line 22 and ending on line 33 with the following:

> Fig. 1A is a simplified diagram of a database system 1000 according to an embodiment of the present invention. This diagram is merely an example and should not limit the scope of the claims herein. One of ordinary skill in the art would recognize many other variations, modifications, and alternatives. Database system 1000 includes a variety of techniques for processing images from biological cells, e.g., fixed, living, and dead cells, and cell portions. As shown, images are acquired 1001. These images can be from a single frame or multiple frames. As merely an example, an image processing system may analyze such images. An example of such an image processing system is described below, but should not be construed as limiting certain claims. A further example of processing techniques is described in more detail in U.S. Serial No. **09/311,890** [_____ (Attorney Docket No. 19681-000200)], noted above. Each image is of a cell portion or a plurality of portions, which are digitized representation(s).

At page 45, please **replace** the paragraph beginning at line 23 and ending at line 28 with the following:

> An example of a MatLab program called "AnalyseDNA" that takes as an input an unlimited number of images, identifies individual objects in these images based on either their intensities, or based on edge-detection algorithms, and extracts a number of morphological and intensity characteristics of these objects. A copy of this program is described in U.S. Application Serial No. **09/310,879** [_____ (Attorney Docket No. 19681-000100)], which has been noted.